

Hyperventilation during exercise: independence on exercise-induced bronchoconstriction in mild asthma

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Ventilatory gas exchange during exercise was compared in patients with mild asthma (11 females and 11 males), hyperventilation syndrome (HVS, 11 females), and healthy subjects (11 females and 11 males) in order to assess hyperventilation during exercise and its association with exercise-induced bronchoconstriction. The asthmatics showed decreased working capacity and decreased maximal oxygen consumption, with no evidence of limitation due to impairment of ventilatory capacity. Ventilatory equivalents for CO₂ and O₂ ($\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$) at rest did not differ between the controls and asthmatics, but they were significantly elevated in HVS. In female asthmatics, ventilatory equivalents during exercise were significantly ($P<0.05$) elevated compared with those of healthy subjects; in female controls, $\dot{V}E/\dot{V}CO_2$ was 30.1 ± 3.3 at low exercise and 27.4 ± 6.5 at maximal exercise. In female asthmatics, the corresponding figures were 34.9 ± 6.1 and 36.7 ± 5.3 . Furthermore, $\dot{V}E/\dot{V}CO_2$ individually related to percent of maximal oxygen consumption ($\dot{V}O_{2\max}$) was significantly increased in female asthmatics both at low and high $\dot{V}O_2$. The highest ventilatory equivalents were obtained in HVS, 41.7 ± 6.7 and 43.9 ± 0.9 , respectively. Significant exercise-induced bronchoconstriction (decrease of FEV₁ >15%) was found in 50% of the asthmatics. The ventilatory equivalents did not correlate with exercise-induced changes in FEV₁ ($r^2<0.3$). Mild exercise-induced hyperventilation which was observed in mild female asthmatics, did not appear to be related to exercise-induced bronchoconstriction.

Introduction

Gas exchange patterns during maximal exercise testing in severe restrictive and obstructive pulmonary diseases include decreased peak oxygen consumption, decreased breathing reserve and increased dyspnoea index (1–7). Previous studies with asthmatics have shown normal or nearly normal cardiorespiratory responses to exercise (8,9). In mild asthma, the impact of gas exchange parameters on exercise-induced bronchoconstriction has not been evaluated previously.

Measurement of ventilatory equivalents for oxygen and carbon dioxide ($\dot{V}E/\dot{V}O_2$, $\dot{V}E/\dot{V}CO_2$) provides information about adaptation of ventilation to metabolic needs. In healthy individuals, ventilatory equivalents during a work-conducted exercise test increase slightly beyond the anaerobic threshold (10). In hyperventilation syndrome (HVS), ventilation in relation to O₂ consumption and CO₂ production is

usually elevated markedly during exercise (11–13). Ventilatory equivalents usually show an inverse correlation with the arterial carbon dioxide tension (PCO₂) level during exercise (13); therefore, they can be used as a diagnostic test to assess unexplained respiratory symptoms.

The aim of the present study was to evaluate the association of exercise-induced bronchoconstriction with the tendency of hyperventilation in mild asthma. Furthermore, ventilatory equivalents between asthmatics, healthy subjects and patients with hyperventilation syndrome were assessed.

Methods

CHARACTERISTICS OF THE PATIENTS

Twenty-two patients with mild asthma (AB) (11 females and 11 males) and 11 patients with hyperventilation syndrome (HVS) (11 females) were studied. Other cardiorespiratory and metabolic diseases, such as hypertension, coronary artery disease, diabetes, remarkable obesity (BMI>30), other pulmonary diseases and psychiatric illnesses were excluded. Successful patients with previously confirmed asthma, who visited the lung function laboratory with FEV₁ $\geq 75\%$ of predicted, were included in the study. The

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HVS group included female patients with clinically typical (11–13) HVS documented previously by blood gases (PCO_2 below 4.5, $pH > 7.45$ and normal or high PO_2) (13). In the HVS group, asthma had been excluded by spirometric testing and diurnal peak flow measurements for 2 weeks, and exercise-induced asthma had been excluded by FEV_1 recordings before and after the exercise test (13). Healthy subjects were from the hospital staff and were matched according to age, sex and weight with the patients.

The anthropometric and lung function characteristics of the patients and healthy subjects are expressed in Table 1. Four AB patients used inhaled sympathomimetics only, 18 used inhaled corticosteroids, and four had been prescribed theophyllin in addition to sympathomimetics and inhaled corticosteroid. The HVS patients had not been using any medication for at least 6 weeks.

PULMONARY FUNCTION TESTS

Flow-volume spirometry with a rolling seal spirometer (CPI 220) connected to a microcomputer system (Medikro 202, Kuopio, Finland) was used to measure forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1) and maximal instantaneous flow at 50% of FVC (MEF_{50}). The results were taken from the envelope curve and compared with the reference values of Viljanen (14). FEV_1 was measured before and after the exercise test with a microspirometer (Micro Medical Instruments Ltd, U.K.) (15). FEV_1 was recorded before the exercise and at 1, 4 and 10 min after the exercise. A decrease of more than 15% in FEV_1 after exercise compared with the pre-exercise value was considered to be significant.

EXERCISE PROTOCOL

Exercise testing with an electrically braked bicycle ergometer (Bosch) starting from 40 W (women) or 50 W (men) was used. Controls as well as the asthma and HVS patients rested for 10 min before they were tested. Furthermore, all subjects were sitting on the bicycle wearing the face mask for at least 5 min before the exercise test was started. The relative humidity of the inhaled room air was $36 \pm 3.0\%$. The load was increased at 3-min intervals (40 or 50 W steps), and the total duration of the exercise varied between 8 and 17 min. Arterial oxygen saturation before and during the exercise was monitored from a finger with a pulse oximeter (Biox 3700, Ohmeda, U.S.A.). Blood pressure was measured at every level of the exercise from the left arm. Electrocardiogram was monitored and recorded continuously with a

computerized ECG device (Case 12, Marquette Inc, U.S.A.). The heart rate was automatically derived from ECG. The target rate of perceived exertion according to Borg's scale was 18–19/20 (16), and the respiratory quotient (RQ) obtained at peak exercise was always over 1.00.

VENTILATORY VARIABLES

The expired air was collected for analysis using a tightly attached face mask (Rudolph exercise stress mask, Hans Rudolph Inc.). Exercise and measurements were started when a stable level of the ventilatory parameters had been achieved at rest. Continuous measurements of minute ventilation ($\dot{V}E$, $l \min^{-1}$), and O_2 and CO_2 partial pressures of the mixed expired air were carried out with an automatic gas exchange device (Ergo-Oxyscreen, Erich Jaeger, Würzburg, FRG) to determine the following variables of the ventilatory gas exchange: oxygen consumption ($\dot{V}O_2$, $l \min^{-1}$), CO_2 outflow ($\dot{V}CO_2$, $l \min^{-1}$), and ventilatory equivalents for O_2 ($\dot{V}E/\dot{V}O_2$) and CO_2 ($\dot{V}E/\dot{V}CO_2$).

STATISTICAL ANALYSIS

Student's two-tailed *t*-test was used in the statistical comparisons between two groups. Variance analysis (ANOVA, Scheffe) was used for comparisons of more than two groups.

Results

Five of 22 controls, 13 of 22 asthmatics and eight of 11 HVS patients considered dyspnoea to be the most important subjective symptom at the end of the exercise. Gas exchange findings during the exercise test are shown in Table 2. Maximum working capacity and oxygen consumption were lower in AB and HVS patients than in healthy controls. No desaturation occurred in any case.

VENTILATORY GAS EXCHANGE

Ventilatory equivalents at rest before exercise were significantly increased in the HVS group, alone, when compared with the values of healthy controls (Table 3). $\dot{V}E/\dot{V}CO_2$ was elevated in female asthmatics during exercise when compared with that of controls; the difference was significant at the work loads of 40 W and 80 W [Fig. 1 (a,b)]. The findings concerning $\dot{V}E/\dot{V}CO_2$ were similar to those of $\dot{V}E/\dot{V}O_2$ [Fig. 1 (c,d)]. $\dot{V}E/\dot{V}CO_2$ values were also plotted in relation to $\dot{V}O_2$. The results, which are shown in Fig. 2(a), confirm significantly elevated $\dot{V}E/\dot{V}CO_2$ in female asthmatics when compared with the corresponding values in control subjects. In addition, $\dot{V}E/\dot{V}CO_2$

Table 1 Anthropometric data and pulmonary function values at rest in controls, asthmatics and patients with hyperventilation syndrome (HVS)

	Control		Asthma		HVS
	Female	Male	Female	Male	Female
Age (years)	40.4 ± 6.3	43.6 ± 7.6	43.7 ± 10.3	44.2 ± 12.6	43.8 ± 10.9
BMI	22.3 ± 2.5	25.7 ± 2.3	26.8 ± 4.6	25.9 ± 4.2	25.9 ± 3.2
FVC (% of pred)	100 ± 10.3	102 ± 11.5	85.0 ± 14.1	100 ± 16.8	98.6 ± 17.7
FEV ₁ (% of pred)	106 ± 9.8	106 ± 12.3	85.0 ± 8.4	95.1 ± 15.0	101 ± 16.9

Values are means ± SD, *n* = 11 in each group.

BMI, Body mass index. Predicted values according to Viljanen *et al.* (14).

Table 2 Gas exchange parameters during exercise in controls, asthmatics and patients with hyperventilation syndrome (HVS)

	Control		Asthma		HVS
	Female	Male	Female	Male	Female
W _{max} (w)	162 ± 47	255 ± 38	108 ± 31*	191 ± 38*	101 ± 37*
$\dot{V}O_{2\max}$ (ml min ⁻¹ kg ⁻¹)	31.3 ± 5.6	37.3 ± 5.3	19.3 ± 4.7*	29.8 ± 6.4*	21.9 ± 7.5*
HR _{max} (l min ⁻¹)	173 ± 8	174 ± 14	162 ± 21	176 ± 17	165 ± 14
BF _{max} (l min ⁻¹)	31.5 ± 4.3	35.0 ± 7.7	36.5 ± 7.8	33.6 ± 7.6	39.4 ± 6.7
$\dot{V}E_{\max}$ (l min ⁻¹)	61.0 ± 19.7	108 ± 24	52.5 ± 14.7	84.7 ± 17.8	64.8 ± 20.8
BR (%)	53.5 ± 7.3	38.6 ± 9.8	42.4 ± 14.3	41.4 ± 15.5	46.4 ± 15.9
RQ	1.12 ± 0.09	1.13 ± 0.13	1.05 ± 0.11	1.07 ± 0.08	1.04 ± 0.06

Values are means ± SD, *n* = 11 in each group; **P* < 0.05 vs. control.

W_{max}, maximal workload attained; $\dot{V}O_2$, O₂ consumption; HR_{max}, maximal heart rate; BF_{max}, maximal breathing frequency; $\dot{V}E_{\max}$, maximal ventilation; BR, breathing reserve; RQ, respiratory quotient.

Table 3 Ventilatory equivalents for O₂ ($\dot{V}E/\dot{V}O_2$) and CO₂ ($\dot{V}E/\dot{V}CO_2$) with the subjects sitting on bicycle before the exercise

	Control		Asthma		HVS
	Female	Male	Female	Male	Female
$\dot{V}E/\dot{V}O_2$	32.4 ± 3.6	30.6 ± 7.1	33.7 ± 4.10	33.0 ± 5.9	41.3 ± 8.2*
$\dot{V}E/\dot{V}CO_2$	41.5 ± 3.0	41.0 ± 8.4	44.2 ± 4.0	43.0 ± 6.3	59.2 ± 3.0*

HVS, hyperventilation syndrome.

Values are means ± SD, *n* = 11 in each group; **P* < 0.05 vs. control and asthma.

related to 40% of $\dot{V}O_{2\max}$ was almost significantly (*P* = 0.055) elevated in asthmatic males, when compared with the control subjects [Fig. 2(b)].

Because ventilatory equivalents during exercise were elevated in female asthmatics suggesting hyperventilation, their ventilatory equivalents were compared with those in HVS females. In HVS patients, $\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$ at rest were significantly higher than in the other groups. When all three groups were compared (Scheffe's *post hoc* test) during

exercise, only the equivalents of the HVS group were significantly elevated (44.8 ± 8.9 for $\dot{V}E/\dot{V}O_2$ and 43.9 ± 7.9 for $\dot{V}E/\dot{V}CO_2$, respectively) (Fig. 3).

At 1 min after exercise, two asthmatic males but no asthmatic females showed exercise-induced bronchoconstriction (decrease of FEV₁ at least 15% from the pre-exercise level). At 4 or 10 min post-exercise, 11 asthmatic patients had exercise-induced bronchoconstriction (seven females and four males). The individual values of ventilatory equivalents of asthmatics

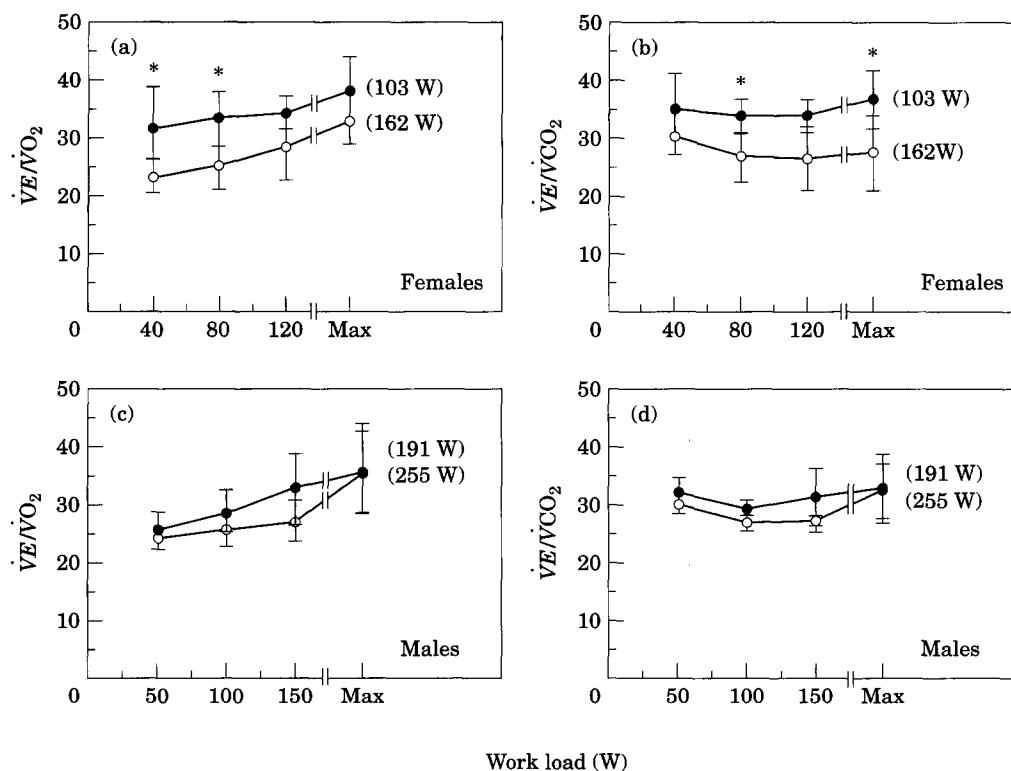


Fig. 1 Ventilatory equivalents for O_2 and CO_2 ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$) in controls (○) and asthmatics (●). Values are means \pm SD from 11 females and 11 males. * $P < 0.05$ (Student's *t*-test). Numbers in parentheses indicate maximal work load attained.

without and with bronchoconstriction are shown in Figs 4 and 5. The ventilatory equivalents did not correlate with the exercise-induced changes in FEV_1 ($r^2 < 0.3$).

Discussion

The results of this study show that mild asthma may be associated with exercise-induced hypoventilation in females, which can be assessed in exercise testing by measuring ventilatory equivalents. Exercise-induced bronchoconstriction and ventilatory equivalents were found not to correlate with each other in mild asthma.

In this study, asthma patients who had normal or nearly normal lung function were selected. For comparison, healthy subjects and patients with HVS were included. Decreased working capacity, which was observed in asthma, was not related to any pathological reason or respiratory limitation although the subjective symptoms at the end of the test included breathlessness in most cases (62% of the asthmatics). Earlier studies have shown that maximal oxygen

consumption and working capacity in mild asthma are normal or slightly reduced (9). Possible reasons for the lowered working capacity in this study may include more sedentary lifestyle, poor fitness and aversion to exercise in many adult asthmatics.

Previous studies have shown that ventilatory equivalents can be used as an aid to assess the adaptation of ventilation during exercise (8, 13, 17, 18). Normal ranges of the ventilatory equivalents at maximal working level in different studies vary between 22–39 for $\dot{V}E/\dot{V}O_2$ and 26–30 for $\dot{V}E/\dot{V}CO_2$ (10, 17). In the study of Blackie *et al.* (18), mean $\dot{V}E/\dot{V}CO_2$ was 30.7, and in a recent study by Eschenbacher and Mannina (19), $\dot{V}E/\dot{V}CO_2$ values over 40 were considered pathological. In the present study, the values of these parameters in healthy controls were within the normal limits published previously. Pre-testing was not used in the present study, but in the author's previous study, it did not have a significant effect on the ventilatory equivalents when this exercise system was used (20). $\dot{V}E/\dot{V}CO_2$ at maximal exercise levels were 27.4 ± 6.5 in female controls and 43.9 ± 9.0 in HVS, respectively. In

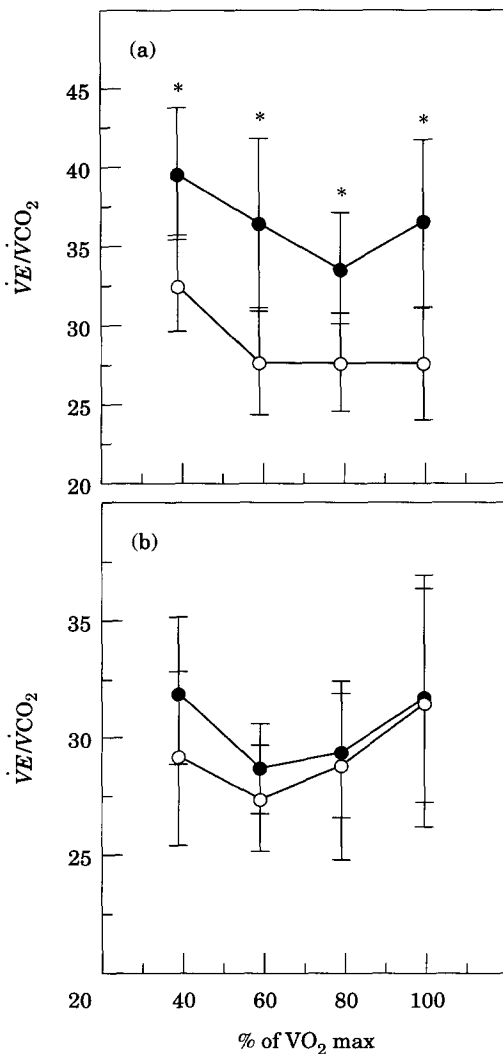


Fig. 2 Ventilatory equivalents for CO₂ ($\dot{V}E/\dot{V}CO_2$) in controls (○) and asthmatics (●) in relation to percent of maximal oxygen consumption ($\dot{V}O_{2max}$). (a) females, (b) males. * $P < 0.05$ (Student's *t*-test).

agreement with earlier studies (10, 17, 18), the ventilatory equivalents were similar in females and males. Ventilatory equivalents in asthmatics were marginally higher than the equivalents in the controls and lower than the equivalents in the HVS group suggesting a tendency to exercise-induced hyperventilation in mild asthma. However, when the equivalents were compared between the controls, asthmatics and HVS patients, only the HVS group differed significantly from the other two groups.

Ventilatory equivalents are good indicators for hyperventilation; both $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$ have

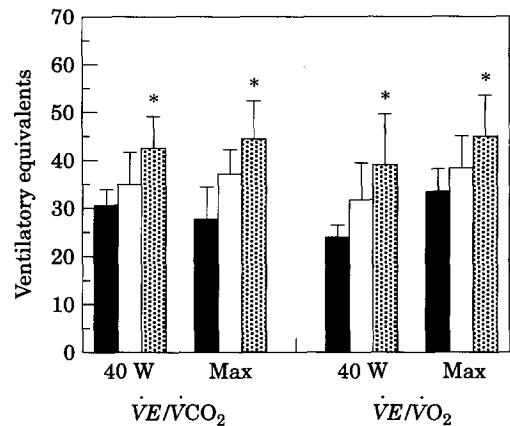


Fig. 3 Ventilatory equivalents for O₂ ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$) in female controls (solid bars), asthmatics (open bars) and female hyperventilation syndrome patients (stippled bars) at low and maximal exercise levels. * $P < 0.05$ vs. controls (Scheffe's *post hoc* test).

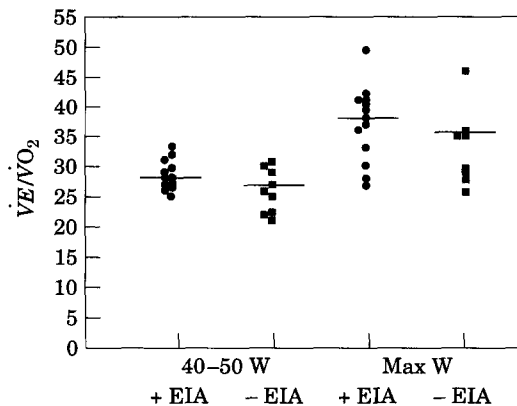


Fig. 4 Ventilatory equivalent for O₂ ($\dot{V}E/\dot{V}O_2$) in asthmatics without (-EIA) or with (+EIA) exercise-induced hyper-reactivity (>15% FEV₁ decline 10 min after exercise). The values are presented at 40-50 W and maximal exercise levels (Max W).

been shown to correlate significantly with $PaCO_2$ during exercise with correlation coefficients over 0.7 (13). In the present study, exercise-induced hyperventilation was found among female asthma patients both at low and high exercise levels, and also when the equivalents were related to the percent of maximal oxygen consumption. Hyperventilation, which was not significant at rest, was noted especially at low exercise levels and was not related to secondary factors such as decreased respiratory capacity, decreased ventilatory reserves or early anaerobic threshold. All asthmatics studied had normal or only marginally decreased ventilatory capacity, which did

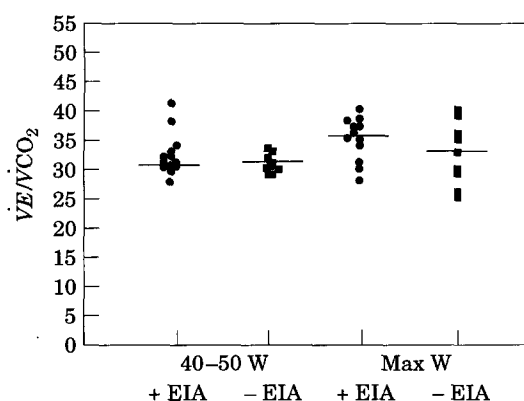


Fig. 5 Ventilatory equivalent for CO_2 ($\dot{V}E/\dot{V}CO_2$) in asthmatics without (- EIA) or with (+ EIA) exercise-induced hyper-reactivity ($>15\%$ FEV_1 decline 10 min after exercise). The values are presented at 40-50 W and maximal exercise levels (Max W).

not limit exercise capacity at maximal exercise level. Elevated ventilatory equivalents in female asthmatics may suggest that hyperventilation is more common among female than male asthmatics. This gender difference has actually been found in hyperventilation syndrome (21). On the other hand, this study was conducted in a small patient group, which was selected from hospital material, and therefore these findings cannot be extrapolated to large unselected groups of asthma patients. Furthermore, the performance status between the female controls and asthmatics differed significantly. Whether the difference in the ventilatory equivalents would disappear if the performance status in these groups is similar, remains unclear. These findings, however, suggest that the working capacity in female asthmatics may be lower than in healthy controls and that hyperventilation may explain some of the dyspnoea symptoms in asthma. Furthermore, the ventilatory equivalents of the HVS patients were markedly higher than the equivalents of the control group.

Hyperventilation during exercise was not associated with exercise-induced bronchoconstriction immediately or 4-10 min after exercise, since there was no correlation between the ventilatory equivalents and changes of FEV_1 after the exercise. The results also showed that exercise-induced excess ventilation did not predispose mild asthmatics to exercise-induced bronchoconstriction if compared with asthmatics without excess ventilation during exercise. Half of the asthmatics in this study showed exercise-induced bronchoconstriction. The effect of the severity of the disease or the therapy to asthma were eliminated by the fact that the asthma group

was very homogenous in terms of lung function and asthma therapy. In the asthma group, only four patients did not use inhaled corticosteroids, two of them had an exercise-induced reaction. Atopy did not predispose exercise-induced reactivity; eight patients had atopy, and only two of them had an exercise-induced reaction.

The mechanisms of hyperventilation in different pulmonary diseases are probably very different. In HVS it has been shown to relate to the central disturbance of the regulation in breathing or to psychological factors (22,23). Increased ventilation which also occurs at rest in moderate asthma has been explained by hypoxia, lung hyperinflation and reflex stimulation of lung mechanoreceptors (24,25). The pathogenesis of exercise-induced asthma is more complicated; it has been widely studied and reviewed previously. Temperature, humidity, hyperventilation and also the release of histamine and various cytokines are important determinants of exercise-induced asthma (26-31). Factors contributing towards exercise-induced hyperventilation and bronchoconstriction in the asthma patients in this study may include excess irritation of the airways, elevated airway cytokine levels, and epithelial cell injury even in mild asthma (32).

In conclusion, mild asthma in females may be associated with exercise-induced hyperventilation, which does not correlate with exercise-induced bronchoconstriction. Ventilatory equivalents in combination with other gas exchange parameters and lung function tests give additional information about factors for dyspnoea in these patients.

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